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REVIEW ARTICLE: RED SEAWEED (KAPPAPHYCUS ALVAREZII) AS A CANDIDATE ANTIOXIDANT IN ESTROGEN DEFICIENCY: LINKING LIPID PEROXIDATION, SUPEROXIDE DISMUTASE, AND THE EVIDENCE GAP IN MENOPAUSE MODELS

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ABSTRACT
Menopause is defined by the permanent cessation of menstruation following loss of ovarian follicular function, and it is accompanied by a sustained fall in 17β-estradiol, a hormone that contributes to redox balance both as a direct radical scavenger and through the expression of antioxidant enzymes. The hypoestrogenic state has been associated with increased lipid peroxidation and reduced antioxidant defence. Red seaweed (*Kappaphycus alvarezii*), cultivated extensively in tropical Indonesian waters including Bali, contains phenolic compounds, flavonoids and sulfated polysaccharides with reported antioxidant activity. To examine the antioxidant potential of *K. alvarezii* in relation to the oxidative imbalance of estrogen deficiency, with particular attention to malondialdehyde (MDA), superoxide dismutase (SOD) and 17β-estradiol as complementary indicators of oxidative damage, enzymatic antioxidant capacity and hormonal status. A narrative review with a structured literature search of PubMed and Europe PMC (2000–2026) was conducted on literature addressing the phytochemistry and antioxidant activity of *K. alvarezii*, the mechanisms linking estrogen deficiency to oxidative stress, and the effects of seaweed extracts on redox biomarkers in experimental models. Twelve cell and animal studies met the eligibility criteria, and four supporting studies were analysed separately. Ethanolic extracts scavenged DPPH more effectively than aqueous extracts (IC_{50} 3.03 versus 4.76 mg/mL). In animals, ethanolic extract lowered MDA and raised SOD and glutathione peroxidase in lead-exposed mice at 800 mg/kg body weight, reduced hepatic thiobarbituric acid reactive substances by 25% and 43% at 150 and 300 mg/kg body weight in carbon tetrachloride-injured rats, and produced dose-dependent hepato- and nephroprotection up to 450 mg/kg body weight against cisplatin, although this supporting study measured no oxidative stress marker. Every in vivo study used a non-menopausal model, and where sex was reported most used male animals. In mammary tumour models in rats, extracts lowered lipid peroxidation and improved antioxidant status, but one study also reported antiestrogenic hormone modulation, so the direction of any effect on estradiol under hypoestrogenic conditions is unresolved. *K. alvarezii* is a biologically plausible antioxidant candidate for the oxidative imbalance that accompanies estrogen deficiency, but no study has tested its ethanolic extract in an ovariectomized model while measuring MDA, SOD and 17β-estradiol simultaneously, and activation of the Keap1–Nrf2–ARE pathway remains a proposed rather than a demonstrated mechanism.

Keywords: 17β-estradiol; *kappaphycus alvarezii*; malondialdehyde; menopause; ovariectomy; superoxide dismutase

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INTRODUCTION

Anti-aging medicine is the branch of medicine concerned with the prevention, early detection and management of ageing and age-related disease, with the aim of preserving physiological function and quality of life as people grow older. It is not understood as an attempt to halt ageing, but as an

effort to modulate the biological mechanisms that underlie age-related damage. Ageing itself represents an accumulation of molecular and cellular damage shaped by intrinsic factors such as genomic, epigenetic, mitochondrial and hormonal change, and by extrinsic factors such as diet, physical activity and environmental exposure. In women the most pronounced hormonal transition occurs at menopause. Epigenetic clock analyses have shown that menopause, including early menopause after bilateral oophorectomy, is associated with accelerated epigenetic age, so estrogen deficiency may be regarded as one of the factors that modify the rate of biological ageing in women (Levine et al., 2016; López-Otín et al., 2023).

The World Health Organization defines menopause as the permanent cessation of menstruation caused by loss of ovarian follicular function, established retrospectively after twelve consecutive months of amenorrhoea and occurring in most women between the ages of 45 and 55 years. Women aged 50 years and over accounted for 26% of all women worldwide in 2021. In Indonesia, data from the 2020 Long Form Population Census published by Statistics Indonesia indicate that in 2022 approximately 40.0 million women were aged 45 years or older, or 29.3% of the female population. The size of this group makes menopause an important women's health issue in an ageing population (Badan Pusat Statistik, 2023; World Health Organization, 2024).

Estrogen, and in particular 17β-estradiol, participates in the regulation of redox balance both as a direct radical scavenger and through its influence on the expression of antioxidant enzymes and on mitochondrial function. When estrogen levels fall, the formation of reactive oxygen species (ROS) may exceed antioxidant defence capacity, producing oxidative stress that damages lipids, proteins and DNA. Malondialdehyde (MDA) is one of the end products of the peroxidation of polyunsaturated fatty acids and is used as a marker of oxidative damage to lipids, whereas superoxide dismutase (SOD) is the first-line antioxidant enzyme that catalyses the dismutation of the superoxide anion into hydrogen peroxide and oxygen. Measuring MDA, SOD and 17β-estradiol together can therefore describe oxidative damage, enzymatic antioxidant capacity and hormonal status within a single experimental design (Cervellati & Bergamini, 2016; Hong et al., 2024; Mas-Bargues et al., 2021; Zheng et al., 2023).

The effect of an intervention on estrogen deficiency needs to be examined under controlled conditions, and the ovariectomized rodent is the model most widely used for this purpose. Bilateral ovariectomy removes the principal ovarian source of estrogen and produces a hypoestrogenic state that resembles surgical menopause. Because hormone loss is abrupt rather than gradual, the model is better described as a model of estrogen deficiency than as a complete replica of the natural menopausal transition. A reduction in estradiol and the manifestations of ovarian hormone deficiency have been reported to be present two weeks after ovariectomy and to persist for several weeks thereafter (Georgieva et al., 2021; Koebele & Bimonte-Nelson, 2016; Rodríguez-Landa, 2022; Yousefzadeh et al., 2020).

Menopausal hormone therapy remains the most effective option for vasomotor symptoms and for the prevention of bone loss, but its use must be matched to age, time since menopause, the type and dose of preparation, and individual risk factors and contraindications. Women with a history of hormone-sensitive malignancy, thromboembolism or active liver disease may be unable to use it, and some women choose not to. These constraints have encouraged the exploration of bioactive candidates that target oxidative balance, including candidates derived from natural sources. Natural origin, however, cannot be assumed to imply safety; efficacy, safety and effects on hormonal pathways must be demonstrated in controlled preclinical research, and such candidates should not be positioned as substitutes for hormone therapy (The 2022 Hormone Therapy Position Statement of The North American Menopause Society Advisory Panel, 2022; Davis et al., 2023; Makary et al., 2026).

One marine material relevant to this question is red seaweed (Kappaphycus alvarezii; Rhodophyta, Solieriaceae), cultivated widely in tropical Indonesian waters including Bali, principally as a source of κ-carrageenan. In trade and in many applied publications in Indonesia the material is known by the commercial name “cottonii” or Eucheuma cottonii. Recent taxonomic work confirms that the cultivated “cottonii” of commerce is Kappaphycus alvarezii, whereas E. cottonii in the strict taxonomic sense has been transferred to the genus Kappaphycopsis. This review therefore uses the accepted name Kappaphycus alvarezii throughout, including when citing earlier studies published under the commercial name (Aguilar et al., 2026; Dumilag & Zuccarello, 2022; WoRMS Editorial Board, 2026).

Kappaphycus alvarezii contains sulfated polysaccharides, phenolic compounds, flavonoids and other constituents that show antioxidant activity, and that activity depends on the extraction solvent. Ethanolic extract has been reported to give a DPPH IC_{50} of 3.03 mg/mL, lower than the 4.76 mg/mL of the aqueous extract, and an ethanolic extract of the same material from Lemukutan Island waters in West Kalimantan also showed antioxidant and anti-inflammatory activity. Radical-scavenging activity in a chemical assay does not, however, describe biological effects within a living organism. Seaweed composition also varies with cultivation site, season, harvest age, post-harvest handling and extraction procedure, so material from Bali needs to be characterised in the batch actually used and tested in vivo (Das et al., 2023; Rupert et al., 2022; Sofiana et al., 2021; Suresh Kumar et al., 2008).

Animal evidence on K. alvarezii extract comes so far from non-menopausal models. In male Wistar rats exposed to coal dust, a dose of 300 mg/kg body weight was associated with lower pulmonary MDA, while in rats with carbon tetrachloride liver injury an ethanolic extract at 150 and 300 mg/kg body weight reduced hepatic MDA without accompanying measurement of SOD. In male Wistar rats given cisplatin, ethanolic extract at 250, 350 and 450 mg/kg body weight for 30 days produced the greatest hepatic and renal protection at 450 mg/kg body weight, whereas in male mice exposed to lead acetate only the 800 mg/kg body weight dose lowered MDA and raised SOD and glutathione peroxidase. Differences in species, sex, injury model, tissue examined and preparation mean that an effective dose for estrogen deficiency cannot yet be established (Kania et al., 2013; Natarajan et al., 2023; Vun-Sang et al., 2024; Wardani et al., 2017). On this basis, the present review examines the antioxidant potential of Kappaphycus alvarezii in relation to the oxidative imbalance that accompanies estrogen deficiency, by considering its phytochemical composition, the mechanisms that link hypoestrogenism to lipid peroxidation and reduced enzymatic defence, the experimental evidence available from animal and cell models, and the methodological gaps that remain before a protective effect in menopause can be claimed.

METHOD

This literature review was prepared using a narrative approach supported by a structured database search. Primary evidence on Kappaphycus alvarezii was identified by searching PubMed and Europe PMC on 20 November 2026 for records published from 2000 to 2026, using the query ("Kappaphycus alvarezii" OR "Eucheuma cottonii") AND (antioxidant* OR "oxidative stress" OR malondialdehyde OR "superoxide dismutase") applied to titles and abstracts. Google Scholar and the reference lists of relevant articles were searched manually for studies in regional journals not indexed in these databases, and the World Register of Marine Species was consulted for nomenclature. Background literature on menopause and the ovariectomy model, oxidative stress biomarkers, the Keap1–Nrf2–ARE pathway and phytoestrogens was identified through targeted searches of the same sources and was selected for relevance rather than screened systematically.

Records from the database search were screened against the following inclusion criteria: original

studies in mammalian animal models or cell cultures that administered a K. alvarezii preparation (whole biomass, extract, fraction, polysaccharide or peptide) and measured at least one oxidative stress or redox biomarker, such as malondialdehyde or lipid peroxidation, superoxide dismutase, catalase, glutathione peroxidase or reactive oxygen species, or reproductive hormones. Records were excluded if they were reviews or preprints; concerned algal physiology, cultivation or use as a plant biostimulant; concerned food products, materials or nanotechnology; used non-mammalian animal models; reported antioxidant data only from chemical assays, phytochemical analysis or cytotoxicity testing, without a redox outcome in cells or animals; or reported no oxidative stress or hormonal outcome. Studies of phytochemical composition and in vitro antioxidant capacity were not reviewed exhaustively but were selected to illustrate the effects of solvent, extraction method and reporting basis. Because earlier studies frequently reported the same organism under the commercial name Eucheuma cottonii, those studies were included and are cited here under the accepted name Kappaphycus alvarezii; this harmonisation of nomenclature does not alter the biological identity of the material reported by the original authors (Aguilar et al., 2026; Dumilag & Zuccarello, 2022).

The database search yielded 103 records (PubMed, 45; Europe PMC, 58). After removal of 51 duplicates, including preprint and secondary-database versions of the same articles, the titles and abstracts of 52 records were screened. Of these, 43 were excluded: 13 reported antioxidant data only from chemical assays, phytochemical analysis or cytotoxicity testing, nine concerned algal physiology, cultivation or plant biostimulant use, six concerned food products, materials or nanotechnology, five were reviews, four reported no oxidative stress or hormonal outcome, three used non-mammalian models and three were preprints. Nine studies met the inclusion criteria, and three further studies were identified through Google Scholar and reference lists (Namvar et al., 2012; Vun-Sang et al., 2024; Wresdiyati et al., 2008), giving 12 studies that form the main body of evidence summarised in Table 1. Table 1 also lists two in vitro studies and two animal studies without redox outcomes that are discussed as supporting evidence. In total, 57 sources were cited in this review: 54 journal articles and three institutional or database sources (the World Health Organization, Statistics Indonesia and the World Register of Marine Species).

The articles obtained were analysed narratively, taking into account the species and sex of the animal, the injury or deficiency model, the part of the organism used, the preparation and solvent, the dose and duration of administration, the tissue examined and the parameters evaluated. Studies using different models or different preparations were retained as supporting evidence but were explicitly distinguished from studies that match the focus of this review, so that the distance between the available evidence and the question of menopause remains visible throughout.

RESULT

Study Selection

The searches retrieved 103 records (PubMed, 45; Europe PMC, 58). After removal of 51 duplicates, the titles and abstracts of 52 records were screened, and 43 were excluded: 13 reported antioxidant data only from chemical assays, phytochemical analysis or cytotoxicity testing; nine concerned algal physiology, cultivation or plant biostimulant use; six concerned food products, materials or nanotechnology; five were reviews; four reported no oxidative stress or hormonal outcome; three used non-mammalian models; and three were preprints. Nine studies were eligible from the database search, and three further eligible studies were identified through supplementary searching (Namvar et al., 2012; Vun-Sang et al., 2024; Wresdiyati et al., 2008), giving 12 included studies (Figure 1). Four supporting studies that did not meet the eligibility criteria are reported separately. In total, the review cites 57 sources: 54 journal articles and three institutional or database sources (the World Health Organization, Statistics Indonesia and the World Register of Marine Species).

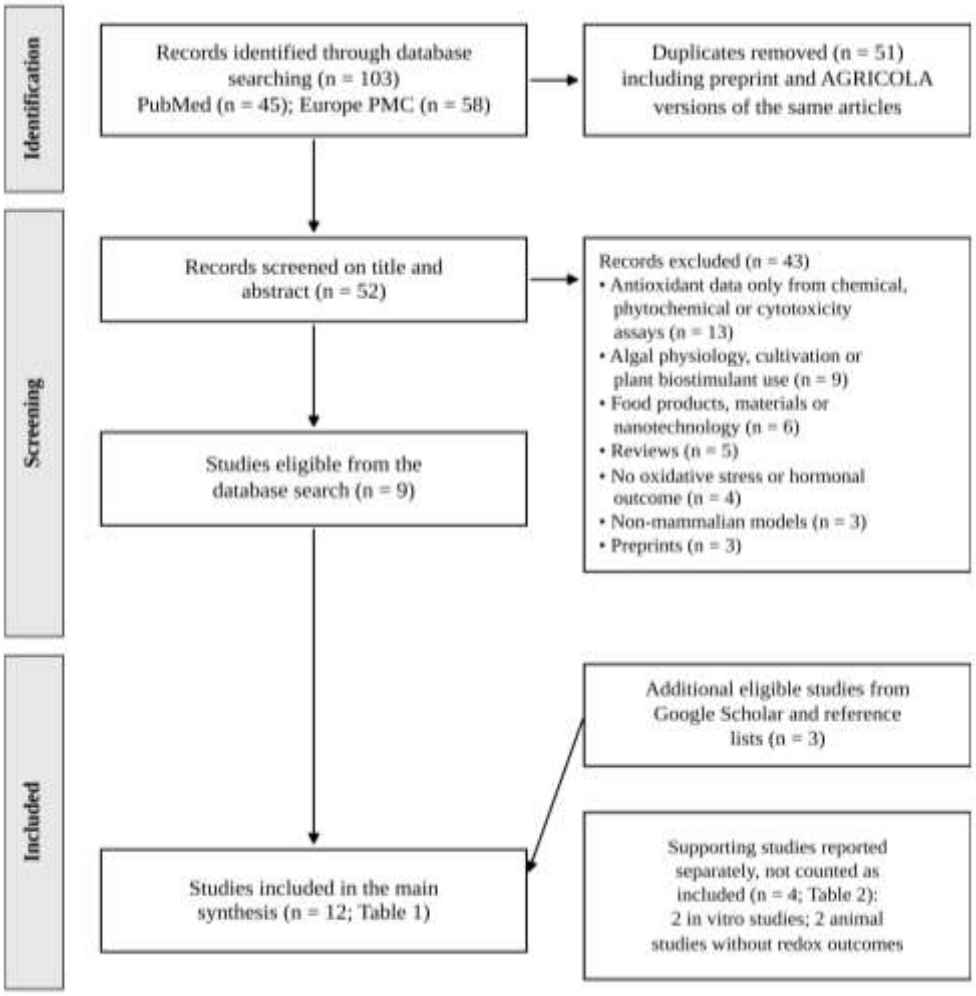

Figure 1. Flow of records through the structured search and selection. Supporting studies did not meet the eligibility criteria and are not counted among the 12 included studies.

Table 1.
Summary of studies on red seaweed (*Kappaphycus alvarezii*), antioxidant activity, and redox or hormonal parameters

Study	Model / induction	Preparation & dose	Parameters	Main findings
Suresh Kumar et al. (2008)	In vitro (DPPH, Fe^{2+} chelation, reducing power)	Ethanol, methanol and aqueous extracts	DPPH IC_{50}, metal chelation	Ethanol IC_{50} 3.03 mg/mL; water 4.76 mg/mL; methanol best Fe^{2+} chelation
Ling et al. (2013)	In vitro	Methanol 80%	Total phenolic and flavonoid content	49.04 mg GAE/100 g and 15.54 mg CE/100 g dry sample
Sun et al. (2022)	HUVEC, H_2O_2-induced oxidative damage	Peptides EP4 and EP5 from protein hydrolysate, 200 μM	ROS, MDA, SOD, GPx	SOD and GPx increased; ROS 60.51% and 51.74%, MDA 75.36% and 64.45% of model
Lai et al. (2026)	HaCaT keratinocytes and dermal fibroblasts, UVB/UVA; UV-irradiated nude mice	Low-molecular-weight polysaccharide (KP-90)	ROS, MDA, SOD, CAT, GPx; MMPs, cytokines	ROS and MDA reduced and SOD, CAT and GPx restored in cells; fewer photoaging signs in mice
Kania et al. (2013)	Male Wistar rats, chronic PM_{10} coal dust, 6 months	Ethanolic extract, 150 or 300 mg/kg BW	Pulmonary MDA, EGFR/MUC5AC signalling	Lower pulmonary MDA and suppressed mucin-related signalling
Saputri et al. (2014)	Rats, chronic PM_{10} coal dust, 6 months	Ethanolic extract, 150 or 300 mg/kg BW	BALF MDA (TBARS), alveolar macrophages	Both doses lowered BALF MDA at the two higher coal-dust doses
Wardani et al. (2017)	Male mice, lead acetate 20 mg/kg BW	Ethanolic extract, 200, 400 or 800	MDA, SOD, GPx, liver enzymes	Only 800 mg/kg BW lowered MDA and raised SOD and GPx

Study	Model / induction	Preparation & dose	Parameters	Main findings
		mg/kg BW, 28 days		
Vun-Sang et al. (2024)	Rats, carbon tetrachloride liver injury	Ethanol 95% Soxhlet extract, 150 or 300 mg/kg BW, 14 days	Hepatic TBARS, CAT, GST, AST/ALT	TBARS fell 25% and 43%; CAT rose 58% and 77%; SOD not measured
Natarajan et al. (2023)	Male Wistar rats, cisplatin 5 mg/kg BW i.p.	Ethanolic extract, 250, 350 or 450 mg/kg BW, 30 days	Liver and kidney biochemistry, histology	Dose-dependent protection, greatest at 450 mg/kg BW; MDA and SOD not measured
Wresdiyati et al. (2008)	Hypercholesterolemic rats	Whole dried biomass, 5% or 10% of feed	Hepatic Cu,Zn-SOD	Improved hepatic Cu,Zn-SOD status; preparation not an ethanolic extract
Wanyonyi et al. (2017)	Rats, high-carbohydrate high-fat diet, 8 weeks	Whole biomass, 5% w/w of feed	Adiposity, blood pressure, plasma lipids, organ structure	Metabolic syndrome parameters improved; MDA and SOD not primary outcomes
Matanjun et al. (2010)	Male Sprague–Dawley rats, high-cholesterol high-fat diet, 16 weeks	Whole seaweed, 5% of feed	Plasma lipids, plasma LPO, erythrocyte GPx and SOD	Plasma lipids and LPO reduced toward normal values
Yulianti et al. (2022)	Male Wistar rats, streptozotocin–nicotinamide diabetes	Active fraction, 11 or 16.5 mg/kg BW, 4 weeks	H_2O_2, renal NOX4, TNFα, NFκB	H_2O_2 fell 65.33% and 66.71% and NOX4 declined; MDA, SOD and estrogen not assessed
Sanjivkumar et al. (2020)	Wistar rats, alloxan diabetes	Native κ-carrageenan, 500, 750 or 1000 mg/kg BW	Renal SOD, CAT, GPx, GST, GSH, LPO	At 1000 mg/kg BW antioxidant enzymes rose and LPO fell; no acute toxicity at 2000 mg/kg BW
Namvar et al. (2012)	Female rats, mammary tumour model	Polyphenol-rich extract, 150 or 300 mg/kg BW, 4 weeks	Antioxidant status, lipid peroxidation, hormones	Antioxidant status improved and lipid peroxidation fell, but hormone modulation was antiestrogenic
Shamsabadi et al. (2013)	Rats, LA-7 mammary tumour	Ethanolic extract, 100 mg/kg BW orally; tamoxifen comparator	Plasma, hepatic and renal MDA; SOD; erythrocyte GSH	MDA lowered and SOD activity improved more than with tamoxifen; tumour growth suppressed

Note: BALF = bronchoalveolar lavage fluid; BW = body weight; CAT = catalase; CE = catechin equivalent; DPPH = 2,2-diphenyl-1-picrylhydrazyl; GAE = gallic acid equivalent; GPx = glutathione peroxidase; GSH = reduced glutathione; GST = glutathione S-transferase; HUVEC = human umbilical vein endothelial cells; IC_{50} = half-maximal inhibitory concentration; LPO = lipid peroxidation; MDA = malondialdehyde; MMPs = matrix metalloproteinases; ROS = reactive oxygen species; SOD = superoxide dismutase; TBARS = thiobarbituric acid reactive substances. No study listed used an ovariectomized model, and none measured MDA, SOD and 17β-estradiol together in an estrogen-deficient state.

Table 2.
Reported phytochemical constituents of red seaweed (*Kappaphycus alvarezii*) on different sample bases

Compound / parameter	Reported content	Unit and basis	Method / solvent	Source
κ-Carrageenan / soluble fibre	34.6	g/100 g dry biomass	Proximate analysis of dry biomass	Wanyonyi et al. (2017)
Total phenolics	1,892 ± 31	mg GAE/100 g dry extract	Folin–Ciocalteu; ethanol 95%, Soxhlet	Vun-Sang et al. (2024)
Total phenolics	339 ± 45	mg GAE/100 g dry sample	Folin–Ciocalteu; 7-day maceration	Das et al. (2023)
Total phenolics (white variety)	49.04 ± 6.05	mg GAE/100 g dry sample	Folin–Ciocalteu; methanol 80%	Ling et al. (2013)
Flavonoids	163 ± 73	mg CAE/100 g dry sample	$AlCl_3$ colorimetry; 7-day maceration	Das et al. (2023)
Flavonoids (white variety)	15.54 ± 1.68	mg CE/100 g dry sample	Colorimetry; methanol 80%	Ling et al. (2013)

Tannins	294 ± 41	mg CAE/100 g dry sample	Vanillin–HCl; 7-day maceration	Das et al. (2023)
Alkaloids	191 ± 58	mg ATE/100 g dry sample	Colorimetry; 7-day maceration	Das et al. (2023)
Steroids	251 ± 15	mg/100 g dry sample	Colorimetry; 7-day maceration	Das et al. (2023)

Note: ATE = atropine equivalent; CAE/CE = catechin equivalent; GAE = gallic acid equivalent. Values expressed as analytical equivalents are not the mass of an isolated pure compound, and figures reported on a dry extract basis cannot be compared directly with figures reported on a dry sample basis. Values from Das et al. (2023) were converted from mg/g to mg/100 g.

DISCUSSION

Estrogen Deficiency as a Driver of Redox Imbalance

Oxidative stress is defined as an imbalance between the production of reactive oxygen species and the capacity of the antioxidant defence system, resulting in oxidative damage to lipids, proteins and DNA. Under physiological conditions ROS are produced in controlled amounts as by-products of aerobic metabolism and take part in signal transduction, regulation of gene expression and immune responses. When production exceeds defence capacity, progressive cellular damage may follow and ultimately trigger apoptosis or necrosis. The species involved include the superoxide anion, hydrogen peroxide, the hydroxyl radical and singlet oxygen, of which the hydroxyl radical is among the most reactive, and the principal intracellular sources are the mitochondrial electron transport chain, NADPH oxidase, xanthine oxidase and cytochrome P450 (Hong et al., 2024; Rauf et al., 2024).

Estrogen contributes to antioxidant defence through several complementary mechanisms. The aromatic phenolic ring of 17β-estradiol allows it to donate a hydrogen atom to free radicals and so to act as a direct scavenger. Through its receptors it influences the expression of antioxidant enzymes and mitochondrial function; in ovariectomized rats, administration of 17β-estradiol preserved mitochondrial function through the ERα/SIRT1/PGC-1α pathway. Estrogen has also been reported to suppress ROS formation from enzymatic sources including NADPH oxidase (Cervellati & Bergamini, 2016; Hong et al., 2024; Tian et al., 2023). When estrogen is withdrawn, these protective mechanisms are disrupted. In a postmenopausal mouse model, mitochondrial damage preceded the appearance of cognitive deficits, indicating that the mitochondrial consequences of estrogen loss are early rather than terminal events. Disrupted mitochondrial function may raise mitochondrial ROS production, lower antioxidant capacity and increase peroxidation of membrane lipids. In postmenopausal women, several studies have reported higher markers of oxidative damage to lipids, proteins and DNA, while in hypoestrogenic rats plasma MDA was lowered by isoflavone intervention. The magnitude of these changes nevertheless varies with species, tissue, duration of estrogen deficiency and measurement method, so results across studies should be compared with caution (Cervellati & Bergamini, 2016; Noviana et al., 2022; Zhao et al., 2021).

Within an anti-ageing framework, menopause is not treated as a single cause of ageing but as a hormonal change that can modify its rate. Oxidative stress intersects with several hallmarks of ageing: ROS can damage DNA including telomeric sequences, can trigger cellular senescence together with the senescence-associated secretory phenotype, and can affect sirtuin-regulated pathways. An intervention that targets oxidative stress is therefore of theoretical interest beyond symptom relief, although any such benefit must be demonstrated rather than assumed (López-Otín et al., 2023; Rauf et al., 2024).

Malondialdehyde and Superoxide Dismutase as Complementary Readouts

Malondialdehyde, with the IUPAC name propanedial, is one of the principal end products of lipid peroxidation. It is formed through a chain of reactions initiated by free radical attack, particularly

by the hydroxyl radical, on the polyunsaturated fatty acids of membrane phospholipids, among them arachidonic acid and docosahexaenoic acid. Peroxidation proceeds through initiation, when a radical abstracts a hydrogen atom from a polyunsaturated fatty acid to yield a lipid radical; propagation, when the lipid radical reacts with oxygen to form a lipid peroxyl radical that abstracts hydrogen from a neighbouring fatty acid and sustains the chain; and termination, when radical species react with one another. The lipid peroxides and endoperoxides formed then fragment into reactive aldehydes including MDA, which is highly reactive and can cross-link proteins and DNA, disturbing cellular structure and function (Mas-Bargues et al., 2021).

MDA is most often measured by the thiobarbituric acid reactive substances assay, in which MDA reacts with thiobarbituric acid under acidic conditions at high temperature to form a pink complex read spectrophotometrically at 532–535 nm. The method is simple, inexpensive and applicable to plasma, serum, urine and tissue. Its specificity is limited, however, because thiobarbituric acid also reacts with other aldehydes and with unrelated compounds present in the sample, so the result is better read as a general index of lipid peroxidation than as a pure MDA concentration. Chromatographic methods offer higher specificity at greater cost, and where the TBARS assay is used, consistency of procedure, standard curve and sample handling determines whether values can be compared between groups (De Leon & Borges, 2020; Mas-Bargues et al., 2021).

Superoxide dismutase is the metalloenzyme that catalyses the dismutation of the superoxide anion into hydrogen peroxide and molecular oxygen through a two-step redox mechanism, and it constitutes the first line of enzymatic antioxidant defence. Mammalian SOD exists as three isoforms: Cu/Zn-SOD (SOD1) in the cytoplasm and mitochondrial intermembrane space, Mn-SOD (SOD2) in the mitochondrial matrix, and extracellular SOD (SOD3) in plasma and extracellular fluid. Under hypoestrogenic conditions a reduced SOD capacity allows superoxide to accumulate and to react with nitric oxide to form peroxynitrite, a strong oxidant that nitrates protein tyrosine residues and damages DNA, so an intervention that preserves SOD activity would be expected to interrupt this cascade (Anwar et al., 2025; Hong et al., 2024; Younus, 2018; Zheng et al., 2023).

How SOD is measured shapes what the result means. Colorimetric assays based on the inhibition of water-soluble tetrazolium salt reduction by superoxide generated in a xanthine–xanthine oxidase system report catalytic capacity in units per millilitre, one unit being the quantity of enzyme that inhibits half of the reduction reaction. Such a value reflects functional capacity, which depends on the presence of metal cofactors and on the integrity of enzyme structure, rather than the immunological concentration of enzyme protein. Serum SOD also represents mainly the extracellular isoform together with enzyme released from cells, and therefore does not necessarily mirror intracellular SOD in a given organ. The same consideration applies to MDA: tissue MDA reflects local organ damage whereas serum MDA reflects systemic peroxidation burden, which is why effect sizes reported in studies of pulmonary or hepatic MDA cannot be transferred directly to a serum-based design (Kania et al., 2013; Peskin & Winterbourn, 2000; Vun-Sang et al., 2024; Younus, 2018; Zheng et al., 2023).

Phytochemistry and Antioxidant Activity of Kappaphycus alvarezii

The principal structural component of *Kappaphycus alvarezii* is κ-carrageenan, a sulfated galactan of the cell wall. In dry biomass analysed by Wanyonyi et al. (2017), the carrageenan or soluble fibre fraction accounted for 34.6 g/100 g dry weight. That figure describes whole biomass rather than an ethanolic extract and may differ with site, season, harvest age and extraction process (Rupert et al., 2022; Wanyonyi et al., 2017). Beyond sulfated polysaccharides, the alga contains phenolics, flavonoids, tannins, alkaloids, glycosides and steroids. Redox-active constituents of this kind can donate electrons or hydrogen atoms, chelate pro-oxidant metals and interrupt the chain reaction of lipid peroxidation, and the magnitude of the activity depends on solvent polarity and on the basis

used to report content. Reported contents are summarised in Table 2. An important caveat applies to every value in that table: a content measured spectrophotometrically must be read as an analytical equivalent, such as gallic acid equivalent, catechin equivalent or atropine equivalent, and not as the mass of an isolated pure compound. Figures expressed per 100 g are comparable only when sample type, solvent, method and weight basis are the same (Das et al., 2023; Ling et al., 2013; Suresh Kumar et al., 2008). The difference between a dry extract basis and a dry sample basis is not a technicality. A total phenolic content of 1,892 mg GAE/100 g of dry ethanolic extract cannot be equated with 339 mg GAE/100 g of dry sample, because the denominator and the extraction process differ. For material from Bali, minimum reporting should include extraction yield, total phenolics, total flavonoids and the content or profile of κ-carrageenan in the batch actually used (Das et al., 2023; Vun-Sang et al., 2024).

Antioxidant activity has been assessed through chemical assays with different underlying principles. Suresh Kumar et al. (2008) reported a DPPH IC_{50} of 3.03 mg/mL for the ethanolic extract and 4.76 mg/mL for the aqueous extract, while Vun-Sang et al. (2024) reported a DPPH IC_{50} of 4,150 ± 0.41 µg/mL for a 95% ethanolic extract. Differences in solvent, extraction method and sample character must be considered before these numbers are set side by side. The choice of ethanol in work of this kind rests on its capacity to extract the phenolic and flavonoid compounds that contribute to radical scavenging, whereas water extracts a greater proportion of water-soluble polysaccharides such as carrageenan. Because earlier studies used ethanol at different concentrations and by different procedures, including 80% ethanol followed by aqueous extraction and 95% ethanol by Soxhlet, both concentration and method should be stated explicitly for results to be comparable (Kania et al., 2013; Rupert et al., 2022; Suresh Kumar et al., 2008; Vun-Sang et al., 2024).

Assays such as DPPH, ABTS, metal chelation and ferric reducing antioxidant power describe different chemical aspects of antioxidant behaviour, but none of them demonstrates an effect within a living organism. Cell and animal studies are required to assess changes in ROS, antioxidant enzyme activity and lipid peroxidation, and to detect possible toxicity. Composition also varies systematically with cultivation conditions, so that material carrying the same species name but originating from different waters may differ in phenolic content, flavonoid content and antioxidant activity. As far as the literature searched here shows, the phytochemical characteristics of *K. alvarezii* from Bali have not been reported specifically, which makes species determination and phytochemical screening of the study batch a precondition for interpretable and replicable results (Das et al., 2023; Lim et al., 2017; Rupert et al., 2022).

Direct Scavenging and the Proposed Keap1–Nrf2–ARE Route

Under basal conditions Nrf2 is bound by Keap1 and directed to the Cul3 ubiquitin ligase complex for proteasomal degradation. Oxidative or electrophilic stress modifies the sensor cysteine residues of Keap1, ubiquitination of Nrf2 decreases, and Nrf2 accumulates, translocates to the nucleus, forms a heterodimer with small Maf proteins and binds the antioxidant response element to regulate cytoprotective genes. Activation of the ARE increases expression of HO-1, NQO1, GCLC/GCLM, GST, GPx and other elements of the cellular reducing system, which are the most consistently reported Nrf2 targets (Baird & Yamamoto, 2020; Ma, 2013).

The connection between Nrf2 and SOD is supported by mammalian evidence. In rat and mouse cardiomyocytes, proteasome inhibitors increased SOD1 expression through Nrf2-dependent ARE activation, and activation of the SOD1 promoter required functional Nrf2. In the brain of mice lacking Nrf2, basal SOD2 was approximately half that of normal mice, indicating a role for Nrf2 in basal SOD2 expression. SOD expression is nevertheless also governed by other factors such as PGC-1α and CREB, so Nrf2 is not its sole regulator. Functionally the systems act in sequence: SOD converts superoxide into hydrogen peroxide, after which catalase and GPx reduce hydrogen

peroxide and lower the ROS burden; when ROS are not contained, membrane fatty acids undergo peroxidation and yield MDA as one of their end products (Baird & Yamamoto, 2020; Boas et al., 2022; Dreger et al., 2009; Gwarzo, 2009).

Phenolic compounds can modulate the Keap1–Nrf2–ARE axis in a range of biological models. Because *K. alvarezii* contains phenolics, flavonoids and sulfated polysaccharides, and because its extracts have been associated with lower MDA or higher antioxidant enzyme activity, Nrf2 activation is a plausible mechanism. On this basis the effect of the extract on SOD can be explained through two complementary routes, shown in Figure 1. The first is direct radical scavenging by phenolic compounds, which lowers the superoxide burden so that SOD capacity is not depleted. The second is modulation of Keap1–Nrf2–ARE, which reinforces downstream antioxidant systems and may support the maintenance of SOD (Ma, 2013; Nabavi et al., 2016; Suresh Kumar et al., 2008; Vun-Sang et al., 2024). This second route must be stated with care. None of the *K. alvarezii* studies summarised here measured Nrf2 directly, and no study has measured nuclear Nrf2, Keap1, HO-1, NQO1 or GCLC/GCLM after administration of the extract. The pathway is therefore best positioned as a theoretical framework for interpreting changes in MDA and SOD rather than as a demonstrated mechanism, and any causal claim about Nrf2 involvement would require direct measurement of these targets (Baird & Yamamoto, 2020; Nabavi et al., 2016).

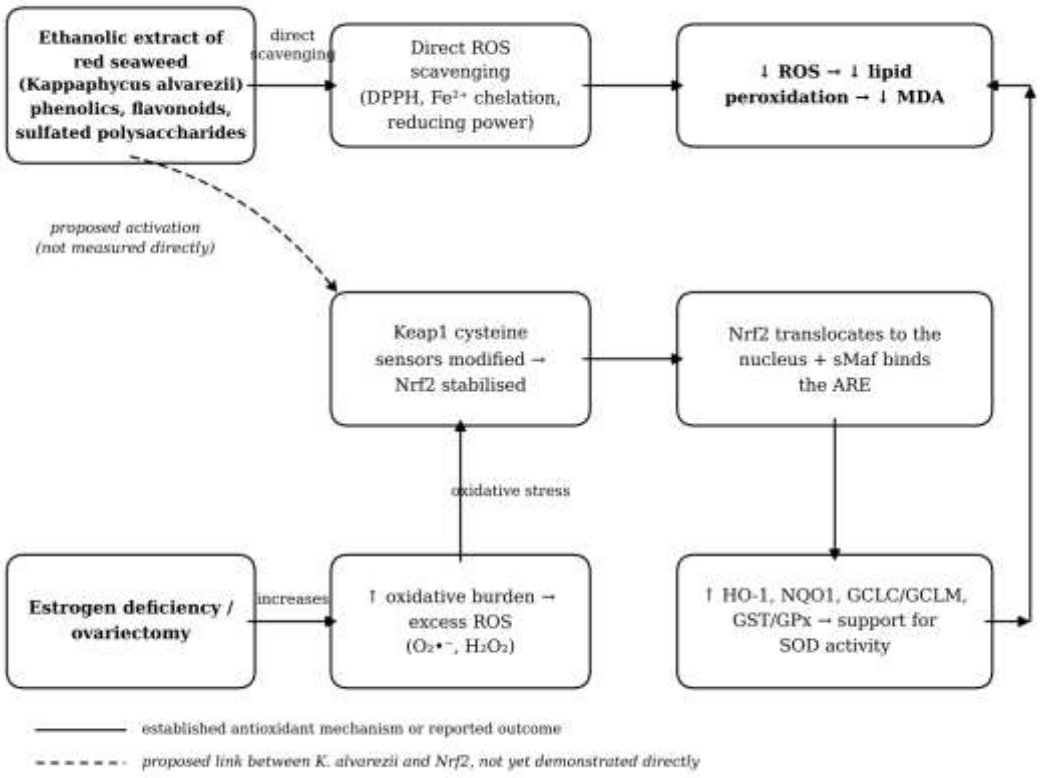

Figure 2. Schematic of the proposed antioxidant mechanism of red seaweed (*Kappaphycus alvarezii*) in estrogen deficiency. Solid arrows indicate established antioxidant mechanisms or reported outcomes; the dashed arrow indicates the proposed link to the Keap1–Nrf2–ARE pathway, which has not been measured directly for this material. Adapted from Baird and Yamamoto (2020), Ma (2013), and Nabavi et al. (2016).

Evidence from Animal Models: Consistent Direction, Inconsistent Doses

Cellular evidence provides the most mechanistically detailed support. In human umbilical vein endothelial cells exposed to hydrogen peroxide, the peptides EP4 and EP5 isolated from a protein hydrolysate of *K. alvarezii* increased SOD and GPx and reduced ROS to 60.51% and 51.74% and

MDA to 75.36% and 64.45% of the model group. The finding demonstrates cytoprotection, but peptides obtained by hydrolysis are not a standard phytochemical parameter of a crude extract, and the result cannot be equated with the effect of an orally administered ethanolic extract. Similarly, a low-molecular-weight polysaccharide obtained by free-radical degradation reduced ROS and MDA and restored SOD, catalase and GPx in UV-irradiated human keratinocytes and dermal fibroblasts, and lessened signs of photoaging in irradiated nude mice; the finding is relevant to skin ageing but again concerns a chemically modified polysaccharide rather than a crude ethanolic extract (Lai et al., 2026; Sun et al., 2022).

In vivo evidence points in a consistent direction but with an irregular dose pattern. In male mice given lead acetate, ethanolic extract at 800 mg/kg body weight lowered MDA and raised SOD and GPx, whereas 200 and 400 mg/kg body weight did not produce the same improvement. In rats with carbon tetrachloride liver injury, ethanolic extract at 150 and 300 mg/kg body weight reduced hepatic TBARS by 25% and 43% and raised catalase and GST. In male Wistar rats given a single intraperitoneal dose of cisplatin, ethanolic extract at 250, 350 and 450 mg/kg body weight administered orally for 30 days lowered ALT, AST, ALP, bilirubin, cholesterol, triglycerides, urea, uric acid and creatinine and improved hepatic and renal histology in a dose-dependent manner, with the largest reductions at 450 mg/kg body weight, but that study measured no oxidative stress marker and included no extract-only group. Dried biomass at 5% and 10% of the diet for 35 days also improved hepatic Cu,Zn-SOD status in hypercholesterolemic rats, although the preparation was not an ethanolic extract. Studies identified through the structured search point the same way. In rats exposed to coal dust for six months, ethanolic extract at 150 and 300 mg/kg body weight lowered MDA in bronchoalveolar lavage fluid, and native κ-carrageenan from this alga at 1000 mg/kg body weight raised renal SOD, catalase and GPx and lowered lipid peroxidation in alloxan-diabetic Wistar rats. Whole seaweed at 5% of a high-cholesterol, high-fat diet reduced plasma lipid peroxidation in male Sprague–Dawley rats over 16 weeks (Matanjun et al., 2010; Natarajan et al., 2023; Sanjivkumar et al., 2020; Saputri et al., 2014; Vun-Sang et al., 2024; Wardani et al., 2017; Wresdiyati et al., 2008).

Taken together, these studies show that an effective dose depends strongly on species, preparation, injury model and tissue examined, which is why a dose range for an estrogen-deficient model has to be justified rather than inherited. Doses of 150 and 300 mg/kg body weight have precedent in several rat models, and 450 mg/kg body weight has precedent for 30 days of administration in Wistar rats. The dose of 800 mg/kg body weight found effective in mice corresponds to approximately 400 mg/kg body weight in rats when converted on the basis of body surface area using K_m factors of 3 for mice and 6 for rats, which places an upper bound near 450 mg/kg body weight within a defensible range. Such literature-based dose setting is also consistent with the requirement for scientific justification of dose in preclinical pharmacodynamic testing guidelines (Kania et al., 2013; Nair & Jacob, 2016; Natarajan et al., 2023; Vun-Sang et al., 2024; Wardani et al., 2017).

Safety deserves a separate note. The status of *K. alvarezii* as a food does not transfer automatically to a concentrated extract, whose toxicity profile is shaped by solvent, purity, dose, duration of administration and possible contaminants. The studies summarised here used whole biomass at 5% to 10% of the diet for five to 16 weeks or ethanolic extract between 100 and 800 mg/kg body weight in particular models. Native κ-carrageenan from this alga produced no acute toxicity in rats at 2000 mg/kg body weight, although a single-dose test of a polysaccharide says little about repeated administration of an ethanolic extract. Work in an estrogen-deficient model would still need to monitor body weight, behaviour, mortality and indicators of hepatic and renal function (Matanjun et al., 2010; Natarajan et al., 2023; Sanjivkumar et al., 2020; Shamsabadi et al., 2013; Vun-Sang et al., 2024; Wanyonyi et al., 2017; Wardani et al., 2017; Wresdiyati et al., 2008).

Phytoestrogen or Antioxidant? The Unresolved Question of 17β-Estradiol

Phytoestrogens are plant-derived compounds whose steroidal or non-steroidal structure allows them to bind estrogen receptors, producing estrogenic or antiestrogenic effects depending on target tissue, receptor subtype, dose and the prevailing concentration of endogenous estrogen. They are classified as isoflavones, lignans, stilbenes and coumestans, and they bind ERα and ERβ competitively but with an affinity roughly 100 to 10,000 times lower than that of 17β-estradiol. Under conditions of estrogen deficiency they may exert partial estrogenic effects that include modulation of antioxidant gene expression through the Nrf2/ARE axis (Domínguez-López et al., 2020; Liu et al., 2020; Rietjens et al., 2017). *Kappaphycus alvarezii* contains phenolics and flavonoids, but total contents of these two classes do not establish estrogenic activity. Whether an extract can modulate ERα or ERβ depends on the identity, concentration and bioavailability of its active compounds, so receptor interaction has to be demonstrated through compound identification and binding or reporter assays rather than inferred from phytochemical screening (Das et al., 2023; Rietjens et al., 2017).

The available evidence in fact points in an unsettled direction. In female rats with a mammary tumour model, a polyphenol-rich extract of this material improved antioxidant status and lowered lipid peroxidation but was accompanied by hormonal modulation that was antiestrogenic in character. In a second mammary tumour model in rats, an ethanolic extract at 100 mg/kg body weight lowered MDA in plasma, liver and kidney and improved SOD activity more effectively than tamoxifen, but that study was designed to test tumour suppression rather than to characterise estrogenic activity. No data describe the influence of the extract on estradiol under hypoestrogenic conditions. The direction of effect may differ according to baseline hormonal status, dose and target tissue, so a finding obtained in a tumour model cannot be extrapolated to a menopausal model. On this basis 17β-estradiol is best treated as an empirical outcome, evaluated to determine whether a difference between groups exists, without specifying its direction in advance and without treating any difference as evidence that the extract is a phytoestrogen (Namvar et al., 2012; Rietjens et al., 2017; Shamsabadi et al., 2013).

Interpretation of estradiol values requires two further cautions. After ovariectomy the residual estrogen derives mainly from peripheral aromatisation of androgens in tissues such as adipose tissue; a compound acting at the estrogen receptor does not necessarily alter circulating estradiol, and a change in circulating estradiol may instead reflect altered peripheral synthesis or hormone metabolism. In addition, the accuracy of estradiol immunoassays in rodent serum varies widely. An evaluation of nine commercial estradiol immunoassays in mouse serum, including serum from ovariectomized animals, found recovery of added estradiol ranging from under 18% to over 640%, with most kits returning values differing several-fold from gas chromatography–tandem mass spectrometry. Any assay used in this setting therefore needs validation data for rodent serum, cross-reactivity data and a detection limit adequate for the low concentrations found after ovariectomy (Davis et al., 2023; Haisenleder et al., 2011; Rietjens et al., 2017).

What Is Missing and What Should Be Done Next

The studies reviewed here support antioxidant activity of *Kappaphycus alvarezii*, including work published under the commercial name. Dose, preparation, duration of administration, animal sex, source of oxidative stress and tissue examined are nevertheless highly heterogeneous. The models used include diabetes, coal dust exposure, hepatotoxicity from lead, carbon tetrachloride or cisplatin, metabolic syndrome, diet-induced hyperlipidaemia, ultraviolet skin damage and mammary tumour. Most used male animals and examined MDA in organ tissue or lavage fluid, plasma markers of lipid peroxidation were reported in only a few studies, and SOD was not always assessed. The only studies in female animals were mammary tumour models. None addressed estrogen deficiency following ovariectomy, so the existing results cannot describe what this material does under hypoestrogenic conditions (Kania et al., 2013; Lai et al., 2026; Matanjun et al.,

2010; Namvar et al., 2012; Natarajan et al., 2023; Sanjivkumar et al., 2020; Saputri et al., 2014; Shamsabadi et al., 2013; Vun-Sang et al., 2024; Wanyonyi et al., 2017; Wardani et al., 2017; Yulianti et al., 2022).

Three gaps follow from this. First, no study has combined an ethanolic extract of *K. alvarezii*, an ovariectomized model and the simultaneous measurement of MDA, SOD and 17β-estradiol. Second, the direction of any effect on estradiol under estrogen deficiency is unknown, and the only female-animal studies available were mammary tumour models, one of which reported antiestrogenic modulation in a very different hormonal context. Third, activation of Keap1–Nrf2–ARE has been proposed repeatedly but never measured directly for this material, which leaves the mechanistic account incomplete (Baird & Yamamoto, 2020; Namvar et al., 2012; Shamsabadi et al., 2013; Vun-Sang et al., 2024).

Future work should therefore evaluate an ethanolic extract in an ovariectomized rodent model with the material characterised in the batch used, including extraction yield, total phenolics, total flavonoids and carrageenan content, and with species identity confirmed by determination and a voucher specimen. Dose selection should be justified from existing animal precedent and interspecies conversion rather than assumed, and the timing of intervention should follow rather than precede the establishment of the hypoestrogenic state, so that surgical stress is not confounded with hormone deficiency. Outcomes should include MDA and SOD together, since a rise in MDA accompanied by a fall in SOD describes an imbalance that neither parameter conveys alone, with 17β-estradiol measured by an assay validated for rodent serum. Where a causal claim about mechanism is intended, nuclear Nrf2, Keap1, HO-1, NQO1 or GCLC/GCLM should be measured directly, and uterine weight may serve as an additional, though only loosely correlated, confirmation of the estrogen-deficient state (Baird & Yamamoto, 2020; Haisenleder et al., 2011; Nair & Jacob, 2016; Rodríguez-Landa, 2022).

CONCLUSION

Red seaweed (Kappaphycus alvarezii) contains phenolic compounds, flavonoids and sulfated polysaccharides with antioxidant activity demonstrated in chemical assays, in endothelial and skin cells and in several animal models of oxidative injury. These properties are theoretically relevant to menopause, where the loss of 17β-estradiol removes both a direct radical scavenger and a regulator of antioxidant enzyme expression, and where lipid peroxidation measured as MDA and enzymatic defence measured as SOD move in opposite directions.

The evidence nevertheless stops short of the question. Studies that measured MDA and SOD mostly used male animals and non-hormonal injury models; the studies that used female animals examined mammary tumour models, and one of them reported antiestrogenic rather than estrogenic hormone modulation; and the rat study that tested ethanolic extract up to 450 mg/kg body weight for 30 days measured no oxidative stress marker at all. No study has tested an ethanolic extract in an ovariectomized model while measuring MDA, SOD and 17β-estradiol simultaneously, and the Keap1–Nrf2–ARE pathway invoked to explain the effect on SOD has not been measured directly for this material. K. alvarezii is therefore a biologically plausible and locally abundant candidate for the oxidative imbalance of estrogen deficiency, but its protective effect in menopause remains to be demonstrated rather than assumed. By consolidating scattered evidence on phytochemistry, redox biomarkers and hormonal interpretation, and by naming the methodological gaps precisely, this review provides a conceptual basis for the experimental work that would be required to close them.

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